

**CLAIMS:**

1. An improved method for the preparation of montelukast acid sodium salt thereof in amorphous form, which comprises:
  - (a) generating the dilithium dianion of 1-(mercaptomethyl)cyclopropane acetic acid, (IX) by reacting with alkyl lithium,
  - (b) coupling the said dianion with wet mesylate of formula (VIII) to get montelukast acid (VI) in crude form,
  - (c) obtaining DCHA salt (X) in crude form by adding dicyclohexylamine (DCHA) to crude acid obtained in the above step (b),
  - (d) purifying and converting the said DCHA salt (X) in crude form, to montelukast acid in pure form, and
  - (e) reacting the pure montelukast acid in a polar protic solvent with a source of sodium ion followed by evaporating the solvent and triturating of the residue with non-polar water immiscible solvent to obtain the title compound.
2. An improved method for the preparation of montelukast acid and sodium salt thereof in amorphous form, which comprises:
  - (a) coupling the 1-(mercaptomethyl)cyclopropane acetic acid (IX) with mesylate of formula VIII in the presence of alkyl lithium to get montelukast acid (VI) in crude form,
  - (b) obtaining DCHA salt (X) in crude form by adding dicyclohexylamine (DCHA) to crude acid obtained in the above step (a),
  - (c) purifying and converting the said DCHA salt (X) in crude form, to montelukast acid in pure form, and
  - (d) reacting the pure montelukast acid in a polar protic solvent with a source of sodium ion followed by evaporating the solvent and triturating of the residue with non-polar water immiscible solvent to obtain the title compound.

3. An improved method as claimed in claims 1 and 2 where in, the dilithium dianion is prepared by known method preferably according to the process described in US Patent No. 5, 614,632.
4. An improved method as claimed in claims 1 and 2 where in the alkyl lithium used is methyl, ethyl, propyl, butyl, isobutyl and n-hexyl lithium preferably n-butyl lithium.
5. An improved method as claimed in claims 1 and 2 where in, the mesylate is prepared by reacting corresponding diol with methane sulfonyl chloride in an inert solvent such as toluene and acetonitrile or etheral solvent like THF in presence of tertiary amine preferably N-N di-iso propyl ethyl amine.
6. An improved method as claimed in any preceding claims where in, the mesylation is carried out at  $-40$  to  $-25^{\circ}\text{C}$ .
7. An improved method as claimed in any preceding claims where in the amount of 1-(mercaptomethyl)cyclopropane acetic acid or dilithium dianion of the said acid or alkyl lithium is determined on the basis of Loss on Drying (LOD) analysis of mesylate.
8. An improved method as claimed in claims 1 and 2 where in the coupling is effected by Slow addition of a cooled ( $-30$  to  $+5^{\circ}\text{C}$ ) solution of wet mesylate (VIII) in THF to a cooled ( $-30$  to  $+5^{\circ}\text{C}$ ) stirred and mixed solutions of IX and n-butyl lithium in hexanes and THF.
9. An improved method as claimed in claims 1 and 2 where in the coupling is effected by slow addition of n-butyl lithium in hexanes ( $-30$  to  $+35^{\circ}\text{C}$ ) to a cooled ( $-30$  to  $+5^{\circ}\text{C}$ ) stirred and mixed solutions of wet VIII and IX in THF.
10. An improved method as claimed in claims 1 and 2 where in the coupling is effected slow addition of cooled ( $-30$  to  $+5^{\circ}\text{C}$ ) solution of IX to a cooled ( $-30$  to  $+5^{\circ}\text{C}$ ) stirred and mixed solutions of wet VIII and n-butyl lithium in THF and hexanes.

11. An improved method as claimed in claims 1 and 2 where in the coupling is effected by slow addition of a cooled (-30 to +5°C) solution of a mixture of **IX** and n-butyl lithium in hexanes and THF to a cooled (-30 to +5°C) and stirred solution of wet **VIII** in THF.
12. An improved method as claimed in claims 1 and 2 where in the coupling is effected by slow addition of a cooled (-30 to +5°C) solution of a mixture of **VIII** and **IX** to a cooled (-30 to +5°C) and stirred solution of n-butyl lithium in hexanes and THF.
13. An improved method as claimed in claims 1 and 2 where in the coupling is effected by slow addition of a cooled (-50 to -25°C) solution of a mixture of **VIII** and n-butyl lithium in THF and hexanes to a cooled (-30 to +5°C) and stirred solution of **IX** in THF.
14. An improved method as claimed in claims 1 and 2 where in the coupling is effected by parallel and concurrent slow addition of solutions of n-butyl lithium (-30° to +35°C) in hexanes and 9 (at -30 to +35°C) in THF to a cooled (-30 to +05°C) solution of **VIII** in THF.
15. An improved method as claimed in claims 1 and 2 where in the coupling is effected by parallel and concurrent slow addition of solution on n-butyl lithium (-30 to +35°C) in hexanes and a cooled solution (-30 to +05°C) of wet **VIII** in THF to a cooled and stirred solution (-30 to +05°C) of **IX** in THF.
16. An improved method as claimed in claims 1 and 2 where in the coupling is effected by parallel and concurrent slow addition of a cooled (-35 to +05°C) solution of **VIII** in THF and **IX** in THF (at +30 to +35°C) to a cooled (-30 to +05°C) and stirred solution of n-butyl lithium in hexanes and THF.
17. An improved method as claimed in claims 1 and 2 where in the coupling is effected at a temperature ranging from -30 to +30, preferably -20 to +10 and more preferably  $-5 \pm 2$  °C.

18. An improved method as claimed in claims 1 and 2 where in the coupling is effected under stirring for a period of 1 to 18 preferably 12 to 16 hours.
19. An improved method as claimed in claims 1 and 2 where in the DCHA used in step (c) and step (b) respectively, is neat. The reaction is carried out in ethyl acetate, under stirring and the product so obtained is washed with ethyl acetate and hexane.
20. An improved method as claimed in claims 1 and 2 where in the DCHA salt is purified by washing with toluene and hexane.
21. An improved method as claimed in claims 1, 2, and 20 where in the toluene used for washing ranger from 5 to 20 times preferably 8 to 10 times v/w wrt wet DCHA salt.
22. An improved method as claimed in claims 1 and 2 where in conversion of DCHA salt to montelukast acid (VI) and its purification is carried out by treating the said salt with acid in presence of water miscible organic solvent.
23. An improved method as claimed in claims 1,2 and 22 where in the acid used is organic or inorganic or mixture thereof.
24. An improved method as claimed in preceding claims wherein the organic acid used is any long chain acid having  $C \cong 8$  such as acetic acid, n-propionic acid, iso-propionic acid, n-butyric acid, and iso-butyric acid.
25. An improved method as claimed in preceding claims wherein the inorganic acid used is mineral and or halo acid like sulfuric, nitric, phosphoric, polyphosphoric, hydrochloric, hydrobromic, hydroiodic and hydrofluoric acid.
26. An improved method as claimed in preceding claims wherein the strength of acid used is 0.1M to 10M preferably 2M.
27. An improved method as claimed in preceding claims wherein the water miscible solvent used is toluene, benzene, ortho and para xylene, methyl or ethyl acetate preferably toluene.

28. An improved method as claimed in preceding claims wherein the treatment with acid is effected at 0 to 40°C, at a pH of about 4-6 for 2 to 12 hrs preferably for 4 to 6 hrs.
29. An improved method as claimed in claims 1 and 2 wherein the purification is carried out by treating DCHA salt (X) with water immiscible halogenated polar solvent(s) followed by recovering solvent and crystallizing with non polar solvents.
30. An improved method as claimed in claim 29 wherein the water immiscible halogenated polar solvent used is dichloromethane, 1,2-dichloroethane, chloroform or mixture thereof.
31. An improved method as claimed in claim 29 and 30 wherein the recovery of water immiscible halogenated polar solvent is effected to 1/3<sup>rd</sup> of its volume.
32. An improved method as claimed in claim 29 to 31 wherein the non polar solvent used is n-pentane, cyclopentane, cyclohexane, n-hexane, hexanes, cycloheptane, n-heptanes, heptane, diethyl ether, di-isopropyl ether, dibutyl ether, methyl tertiary butyl ether, benzene, toluene, ortho and para xylene, methyl acetate and ethyl acetate.
33. An improved method as claimed in claim 29 and 30 wherein the solvent is completely recovered.
34. An improved method as claimed in claim 29, 30 and 33 wherein the solvent used for crystallization is such as diethyl ether, di-isopropyl ether, methanol, ethanol, n-propanol, iso-propanol, butanol, iso-butanol, methyl tertiary butyl ether, benzene, toluene, ortho and para xylene.
35. An improved method as claimed in claim 29, to 34 wherein the reaction is performed at 10 to 30°C.
36. An improved method as claimed in claims 1 and 2 wherein the purification is carried out by treating DCHA salt (X) with aqueous water miscible solvents followed by recovering the acid of formula VI with either precipitation using water or extraction with polar organic solvent.

37. An improved method as claimed in claim 36 wherein the water miscible solvent used is alkanol such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, dimethylformamide, dimethylacetamide and dimethylsulfoxide.
38. An improved method as claimed in claim 36 and 37 wherein the polar solvent used is selected from methylene chloride, chloroform and 1, 2-dichloroethane, methyl acetate, ethyl acetate, benzene, toluene or ortho and para xylenes.
39. An improved method as claimed in claim 36 to 38 wherein the crystallization is carried out using common non polar aliphatic and alicyclic organic solvents like cyclopentane, n-pentane, and their higher homologues when extraction is performed with polar solvent.
40. An improved method as claimed in claims 1 and 2 where in polar protic solvent used in steps (e) & (d) respectively is lower aliphatic alcohol such as methanol, ethanol.
41. An improved method as claimed in claims 1 and 2 where in the sodium hydroxide is used as source of sodium.
42. An improved method as claimed in claims 1 and 2 where in the reaction in steps (e) & (d) is effected at 5 to 50°C preferably 35 to 40°C.
43. An improved method as claimed in claims 1 and 2 wherein the Montelukast sodium (I) in amorphous form obtained by the process disclosed in the present invention confirms powder X-Ray Diffraction (XRD) Pattern shown in Figure-1.